Docket No.: 5979-0107PUS1
(Patent)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application of:	Alessandro LAMBIASE		
Application No.:	09/890,088	Confirmation No.:	6075
Filed:	July 26, 2001	Art Unit:	1647
For:	METHOD OF TREATING INTRAOCCULAR TISSUE PATHOLOGIES WITH NERVE GROWTH FACTOR	Examiner:	C. Woodward

***DRAFT* AMENDMENT UNDER § 1.116**

NOT FOR ENTRY

FOR DISCUSSION PURPOSES ONLY

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INTRODUCTORY COMMENTS

In reply to the Office Action dated March 10, 2011, the following amendments and remarks are respectfully submitted in connection with the above-identified application.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Attachments: Exhibits A-K

AMENDMENTS TO THE CLAIMS

1-12. **(Canceled)**

13. **(Currently Amended)** A method for the treatment of a pathology affecting internal tissues of an eye selected from the group consisting of scelra, ~~ciliary bodies, crystalline lens,~~ retina, and optic nerve, ~~vitreous body, and choroidea,~~ comprising:

(1) identifying a subject in need of treatment of the pathology; and

(2) topically applying a composition comprising from 200 to 500 μg/ml of nerve growth factor over an ocular surface of the subject to cause an increase in the amount of nerve growth factor in the sclera, retina, and optic nerve, wherein an effective amount of ~~contacting the tissues with~~ the nerve growth factor is provided to said tissues to treat the pathology, and wherein the pathology is selected from the group consisting of: ~~cataract,~~ optic neuritis, glaucoma, maculopathy, retinitis pigmentosa, myopic retinopathy, macular foramen, ~~uveitis, vitretomy, ocular hypotonia,~~ and scleromalacia~~, perforating trauma of the sclera, and phthysis~~.

14. (Previously presented) The method of claim 13, wherein the composition comprises the nerve growth factor in a pharmaceutically acceptable ophthalmic carrier and is in a form selected from the group consisting of solutions, suspensions, ointments, gels, or creams.

15. (Previously presented) The method of claim 13, wherein the composition is in a form selected from the group consisting of an ocular erodible insert, a polymeric membrane reservoir system to be placed in the conjunctival sac, or in combination with a local bandage and a therapeutic contact lens.

16-17. (Canceled)

18. (Previously Presented) The method of claim 14, wherein the composition is in the form of an ophthalmic solution.

19. (Previously Presented) The method of claim 18, wherein the ophthalmic solution contains from 200-250 μg/ml of nerve growth factor.

20. (Previously Presented) The method according to claim 13, wherein the nerve growth factor is of murine or human origin, or is a human recombinant nerve growth factor.

21-32. (Canceled)

33. (Previously Presented) The method of claim 13, wherein the pathology is a pathology affecting the optic nerve.

34. (Previously Presented) The method of claim 13, wherein the pathology is a pathology affecting the retina.

35-36. (Canceled)

37. (**New**) A method for the treatment of a pathology affecting internal tissues of an eye selected from the group consisting of scelra, retina, and optic nerve comprising:

topically applying a composition comprising from 200 to 500 μg/ml of nerve growth factor over an ocular surface of the subject to cause an increase in the amount of nerve growth factor in the sclera, retina, and optic nerve,

wherein an effective amount of the nerve growth factor is provided to said tissues to treat the pathology, and

wherein the patient has been previously diagnosed with a pathology is selected from the group consisting of: optic neuritis, glaucoma, maculopathy, retinitis pigmentosa, myopic retinopathy, macular foramen, and scleromalacia.

REMARKS

Status of the Claims

Claims 13-15, 18-20, 33-34, and 37 are pending in the present application. Claims 1-12, 16-17, 21-32, and 35-36 are canceled. Claim 13 is amended. Claim 37 is new. Support for the amendment to claim 13 is found throughout the application as originally filed including on pages 8-9, and 11. Support for new claim 37 is found in claim 13. No new matter is entered by way of this amendment. Reconsideration is respectfully requested.

Obviousness-Type Double Patenting Issues

Claims 13, 15, 18-20, and 33 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 8-11, and 13 of co-pending U.S. Application No. 12/064,172, *see* Office Action, page 2.

Applicants submit that if a provisional non-statutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the Examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer, *see* MPEP § 804. The relevant "filing date" for double patenting purposes is the earliest U.S. filing date for patent term calculation.

The instant application has a PCT filing date of January 21, 2000. U.S. Application No. 12/064,172 has a PCT filing date of August 11, 2006. Accordingly, Applicants submit that, in view of the arguments and claim amendments submitted herewith, the only rejection remaining in the instant application is the obviousness type double patenting rejection. Therefore, the Examiner should withdraw the rejection and permit the instant application to proceed to allowance.

Issues under 35 U.S.C. § 103(a)

Claims 13-15, 18-20, 33, and 34 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over JP 10-218787 to Okamoto ("Okamoto I") for the reasons of record, *see* Office Action, pages 3-4. Applicants respectfully traverse.

According to the Examiner, Okamoto teaches methods of treating pathologies of the eye, including glaucoma, by topical administration of Nerve Growth Factor (NGF), *see* page 4 of the Office Action, which issued on July 16, 2010. The Examiner indicates that Okamoto does not describe the specific dosage range as described in the present claims, *see* the instant Office Action, page 3. Nevertheless, the Examiner asserts that an ordinary artisan would have reasonably known that dosages are results-effective variables, which can be optimized.

For the reasons set forth below, Applicants submit that the amended claims are not rendered obvious by Okamoto I. Further, Applicants note that PCT Publication No. WO 98/10785, (Okamoto II), which published on March 19, 1998, includes the subject matter described in Okamoto I plus additional subject matter regarding ophthalmic compositions of neurotrophic factors. Accordingly, the following response will reference the subject matter in Okamoto I and Okamoto II. Applicants note that U.S. Patent No. 6,261,545 corresponds to Okamoto II.

Okamoto I and Okamoto II do not teach or suggest all of the elements of the instant claims

Applicants submit that neither Okamoto I nor Okamoto II teach or suggest all of the elements of the amended claims. In particular, neither Okamoto I nor Okamoto II teach or suggest "topically applying a composition comprising from 200 to 500 μg/ml of nerve growth factor over an ocular surface of the subject to cause an increase in the amount of nerve growth factor in the sclera, retina, and optic nerve, wherein an effective amount of the nerve growth factor is provided to said tissues." There is absolutely no disclosure in Okamoto I or Okamoto II, for example, which expressly states or suggests that NGF reaches the retina or the sclera.

The alleged presence of NGF in the optic nerve described in Okamoto I and II does not suggest the presence of an effective amount of NGF in the retina

Okamoto I and Okamoto II indicate that an NGF drug solution reaches the optic nerve *via* the cornea and an anterior aqueous humor or is scattered in corpus vitreum, *see* paragraph [0052] of the English language machine translation of Okamoto I and column 6, lines 50-54 of U.S. Patent No. 6,261,545. According to Okamoto I and II, the drug solution also reaches the chorioid-suprachoidal space through an iris and a ciliary body, and allegedly reaches the optic nerve where NGF shows an effect, *see* paragraph [0052] of Okamoto I and column 6, lines 59-63 of U.S. Patent

No. 6,261,545. Nevertheless, neither Okamoto I nor Okamoto II suggest that an effective amount of NGF reaches all of the posterior target tissues including the retina and sclera.

At the time of the invention, it was uncertain if a topically applied drug, including a large molecule such as NGF, would reach all of the posterior tissues of the eye, including, for example, the retina. Applicants further submit that at the time of the invention, an ordinary artisan was aware that even if a topically applied drug could, hypothetically, reach the optic nerve in an effective amount, such an observation would not have suggested that the drug was also present, for example, in the retina. It was also uncertain how, or if, an effective amount of NGF could reach, for example, the retina. For instance, it was unclear if NGF could pass by route of the sclera, choroid, choriocapillaris and be capable of permeating the retinal pigment epithelium to reach the retina. It was also uncertain if NGF passed into the retrobulbar space and the optic nerve head and could be retro-transported by the optic nerve to retinal ganglion cells. In view of the foregoing, Okamoto's disclosures regarding the presence of NGF in the optic nerve would not have reasonably suggested to an ordinary artisan that any dosage of NGF could have reached, for example, the retina.

For the Examiner's information, Applicants further note that Okamoto's description that the NGF preparation "is adsorbed from a cornea and transited to an anterior aqueous humor, a part thereof reaches an optic disc", is not possible *see* column 6, lines 51-52 of U.S. Patent No. 6,261,545. Applicants submit that it has been widely demonstrated that NGF does not cross the cornea, *see* Exhibit A, Lambiase *et al.*, *IVOS*, 2005, 46:3800-3806, page 3805, paragraph 2.

Okamoto I and II teach away from the range of NGF specified in the present claims

In *Ex parte Whalen*, 89 USPQ2d 1078, 1083 (BPAI 2008) the limitations in question, molecular weight of a polymer and viscosity of a pharmaceutical composition containing the polymer, were know in the prior art as affecting the properties of the composition. Despite the fact that the properties in question were know to affect the results, **the Board of Appeals held that the invention was not *prima facie* obvious because the prior art suggested that the best results would be achieved outside of the claimed range**. In this regard, the Board of Appeals stated:

> Here, the Examiner has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that those skilled in the art would have considered it obvious to

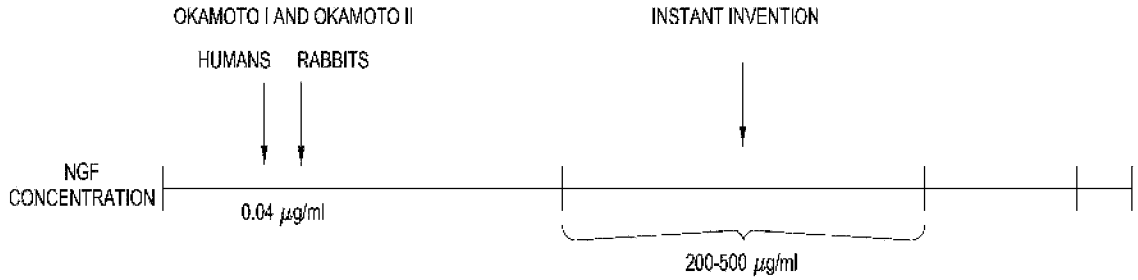
> "optimize the prior art compositions by increasing their viscosity to the level recited in the claims. No reason to have done so is apparent to us based on the record. On the contrary, the references all suggest that low viscosity was a desired property in embolic compositions. … Therefore, Evans' preferred composition has a viscosity less than half of that required by the instant claims.

In the present case, Okamoto I teaches that the dosage of neurotrophic factor ranges from 0.1 μg/250 ml (0.0004 μg/ml) to about 100 mg/250 mls (400 mg/ml), *see* paragraph 51 of Okamoto I. Okomoto II teaches that the dosage of neurotrophic factor may range from about 0.0001 to 0.5% w/v (1 to 5000 μg/ml), or 10^{-3} to 2 x 10^{5} μg/l (10^{-6} to 200 μg/ml), particularly preferably 0.0004 to 0.04% w/v (4 to 400 μg/ml) or 10^{-1} to $1x10^{3}$ μg/l (10^{-4} to 1 μg/ml), *see* column 3, lines 39-42 of U.S. Patent No. 6,261,545 .

Applicants note that the above described ranges refer generally to the dosages of any neurotrophic factor including NGF, BNDF (a brain derived neurotrophic factor), CNTF (a ciliary neurotrophic factor), NT-3 (neurotrophin-3), NT-4/5 (neurotrophin-4/5), NT-6, (neurotrophin-6) and derivatives thereof, *see* column 2, lines 54-66 of U.S. Patent No. 6,261,545, column 3, line 40 of U.S. Patent No. 6,261,545, which refers to "the amount of neurotrophic factor", and *see also* paragraph [0051] and paragraph [0012] in Okamoto I.

In contrast to the generalized dosage ranges for neurotrophic factor described in Okamoto I and Okamoto II, the example sections of these documents specifically discuss a dosage for the topical administration of NGF. In particular, the example of Okamoto I and the Test Examples 1 and 2 of Okamoto II, describe topically administering 0.04 μg/ml of NGF to rabbit eyes. Prior to this administration, the intraocular pressure of the rabbit eyes was increased, resulting in an optic nerve disorder. Okamoto I and Okamoto II state that the optic nerve function was recovered in a week. Further, Example 7 of Okamoto II teaches that topical administration of 0.04 μg/ml of NGF to a glaucoma patient resulted in enlargement of a human patient's visual field.

In view of the teachings in Okamoto I and Okamoto II, Applicants submit that a person of ordinary skill in the art at the time of the invention would not have modified the concentration of the NGF preparation from 0.04 μg/ml to 200 to 500 μg/ml since the range of 200 to 500 μg/ml is so much greater than the alleged effective concentration of 0.04 μg/ml described in Okamoto I and Okamoto II, *see* Figure 1 below.



As held in *Ex parte Whalen*, an invention is not *prima facie* obvious if the prior art suggests that the best results would be achieved outside of the claimed range. Here, Okamoto I and Okamoto II allegedly exemplify that lower concentrations of NGF are effective to restore optic nerve damage and to improve the visual field of a glaucoma patient. Accordingly, Applicants submit that an ordinary artisan would not have considered it obvious to optimize the prior art compositions by increasing the NGF concentration to the much higher level recited in the instant claims. In fact, an ordinary artisan would have been discouraged from increasing the dosage and possibly increasing side effects or toxicity.

Unexpected Effects

1. 200 μg/ml of topically administered NGF enhances survival of retinal ganglion cells

Further, the range of NGF described in the present claims results in effects that could not have been expected by an ordinary artisan at the time of the invention. For example, the concentration range of NGF recited in the claims is surprisingly efficacious in enhancing survival of retinal ganglion cells. As indicated in Exhibit B, dosages of 200 μg/ml of NGF effectively protect retinal ganglion cell (RGC) degeneration, which may occur in a glaucomatous retina, *see* Exhibit B, Lambiase *et al.*, *Proc. Natl. Acad. Sci USA*, 2009, 106:13469-13474, *in particular*, pages 13469-13470, bridging paragraph, which states that a significantly higher biologic effect of 200 μg/ml NGF eye drops in protecting RGC loss in rat retinal sections was observed in comparison to 100 μg/ml NGF. *See also* Exhibit C, Colafrancesco *et al.*, *J. Glaucoma*, 2011, 20:100-108, which further demonstrates that ocular administration of 200 μg/ml NGF may be used to protect degenerating retinal ganglion cells.

2. 200-500 μg/ml of topically administered NGF reach the retina and optic nerve

The range of 200-500 μg/ml as described in the pending claims result in further effects, which could not have been expected by an ordinary artisan at the time of the invention. As noted above, the claimed methods require that nerve growth factor, when topically administered, reaches the optic nerve, retina, and sclera in an effective amount to treat the described diseases. An ordinary artisan, upon reviewing Okamoto I or Okamoto II would not have recognized that this advantageous effect was possible.

Applicants note that the concentration of topically administered NGF exemplified in the Okamoto references, 0.04 μg/ml in human and rabbit, will not reach the optic nerve and retina. According to the available studies on the ocular pharmacokinetics of NGF eye drops, no increase of NGF amounts can be detected in both retina and optic nerve when NGF is administered at 1 μg/ml concentrations (25 times more than the concentration used in Okamoto's examples), *see also* Exhibit D, which describes the passage of NGF through rabbit ocular tissues. Additionally, an accumulation of NGF is not possible because it has been widely demonstrated that NGF is physiologically metabolized. Even at the maximum concentration ever tested (500 μg/ml eye drop), no detectable increase in NGF can be observed after 24 hours.

In contrast to the concentrations of NGF exemplified in Okamoto I and Okamoto II, Exhibit D evidences that an NGF concentration of 200 μg/ml significantly increases the amount of NGF in the retina and the optic nerve over baseline. Concentrations of 1 μg/ml do not increase the amount of NGF in either the retina or the optic nerve over baseline, *see* Exhibit D.

3. 200-500 μg/ml of topically administered NGF crosses the blood ocular barrier

Applicants further submit that NGF crosses the blood ocular barrier when topically administered at a dosage ranging from 200-500 μg/ml. This finding is unexpected. When NGF is administered systemically, NGF does not cross the blood brain barrier. Moreover, NGF does not cross the blood ocular barrier in significant amounts when topically administered at doses outside of the 200-500 μg/ml range. For example, when 10 μg/ml of NGF was topically administered to rats, NGF was not present in the serum, *see* Exhibit A, Lambiase *et al.*, *IVOS*, 2005, 46:3800-3806, in particular Figure 3 and page 3805, right column, paragraph 2. In contrast, when NGF is topically administered at dosages of 200 μg/ml and 500 μg/ml to one eye, NGF is increased in the serum as well as the retina, optic nerve, and sclera of the contralateral

untreated eye of rats, which strongly indicates that NGF passes through the blood-ocular barrier, *see* Exhibit A, pages 3804-3805, bridging paragraph, and page 3805, right column, paragraph 2.

Applicants note that the ability to cross the blood ocular barrier may further contribute to effective amounts of NGF in the retina, in addition to direct passage of NGF through the conjunctiva and sclera and passage through the retro-bulbar space and its retro-transport by the optic nerve to RGS, *see* Exhibit E, Lambiase *et al.*, *Drug News & Perspectives*, 2010, 23:361-367, *in particular* page 365. The ability to cross the blood ocular barrier at the dosages described in the present claims could not have been expected by an ordinary artisan at the time of the invention.

4. Higher concentrations of topically administered NGF are required for therapeutic efficacy

Applicants further submit that an ordinary artisan could not have reasonably expected from Okamoto I and Okamoto II that higher concentrations of topically administered NGF, such as the 200-500 μg/ml concentrations described in the claims, are required to achieve therapeutic efficacy of a variety of ocular diseases including glaucoma. Unexpectedly, topically administered NGF dosages of greater than 100 μg/ml are required to achieve therapeutic efficacy in, for example, optic glioma, glaucoma, and age-related macular degeneration, *see* Exhibit F, Falsini *et al.*, *Neurorehabil Neural Repair*, 2011, 35:512-520, Exhibit G, Chiaretti *et al.*, *Neurorehabil Neural Repair*, 2011, 25:386-390, (electronic publication on February 22, 2011), Exhibit H, Lambiase *et al.*, *Ann Ist Super Sanita*, 2009, 45:439-442 and Exhibit B. *See also* Exhibit E, which is a review article describing the efficacy of topically administered NGF in the treatment of pathologies of the eye and Exhibit I, Sposato *et al.*, *Neuroscience Letters*, 2008, 446:20-24, for a discussion of NGF and NGF-receptors and their role on the optic nerve of rats with experimentally induced elevated intraocular pressure.

An ordinary artisan could not have been reasonably certain that topically administered NGF could have been useful in the treatment of glaucoma from the examples in Okamoto I and Okomoto II.

Animal Model

Applicants submit that a person of ordinary skill in the art at the time of the invention could not have reasonably predicted that topically administered NGF could have been efficaciously used in the treatment of glaucoma from the examples in Okamoto I and Okamoto II. These references use an unpublished animal model, which was obtained by inducing an enormous (60 mmHg) acute increase of intraocular pressure (IOP) by a corneo-scleral sucking device. Applicants submit that such a procedure cannot be considered a model mimicking human glaucoma, which is characterized by a chronic increase of IOP, slightly above the normal levels (21 mmHg), which slowly induces retina and optic nerve progressive damage over several years. Applicants submit that the model of Okamoto resembles an acute ischemic ocular damage instead of typical glaucoma damage. In fact, as a primary parameter of efficacy, Okamato used pupil light reflex reaction, which is never affected in glaucoma, but is a typical sign of optic nerve ischemia or severe trauma. As a secondary parameter, Okamoto used visual evoked potentials (VEPs). Once again, these are constantly affected in severe acute optic nerve injury, but only late and partially affected in glaucoma. Spontaneous recovery of VEPs following ischemic optic nerve damage is frequently observed and shows great variability. Accordingly, in the absence of quantitative data and statistical evaluation, no conclusions on the effectiveness of NGF treatment on the optic nerve injury proposed by Okamoto can be drawn. Moreover, and even more importantly, Okamoto states that "recovery of VEP was… observed", *see* column 8, lines 28-29 of U.S. Patent No. 6,261,545. Applicants submit that recovery of VEP can be observed only in post-ischemic injury, while a spontaneous recovery of VEP is NEVER observed in glaucoma.

In view of the animal model used in Okamoto I and Okamoto II, an ordinary artisan could not have been reasonably certain that any concentration of NGF could have been useful for treating glaucoma.

Human Subject

Okomoto II also describes the effect of NGF in a human glaucoma patient, *see* Example 7 of U.S. Patent No. 6,261,545. However, Applicants submit that an ordinary artisan could not have been reasonably certain from this disclosure that NGF could have been effective in the treatment of glaucoma. Okamoto discloses that he treated only 1 (one) patient with glaucoma with NGF eye drops at a concentration much below that of any published study by the present inventor or others. As noted above, subsequent to Applicant's invention, NGF effects have only been observed at concentrations above 100 μg/ml. Accordingly, Applicants note that Okamoto's claims regarding the efficacy of NGF at 0.04 μg/ml appear unreliable.

Moreover, Okamoto alleges that in order to evaluate the effects of NGF on a single treated patient, he used manual Goldman perimetry. It has been widely proven and published, including in clinical trials, that Goldman perimetry is very much examiner dependent. Goldman perimetry may not be reproducible by another examiner, and it does not have the advantages of a computerized system for storage and comparison to normative data, *see* Exhibit J, Argarwal *et al.*, *Indian J Ophthalmol*, 2000, 48:301-306 and Exhibit K, which includes four scientific abstracts. This is especially true as Okamoto presents data from only 1 (one) patient, therefore, without any kind of statistical analysis.

Additionally, kinetic perimetry may not be as sensitive as static perimetry in detecting early glaucoma defects. In fact, computerized perimetry is unanimously considered the best available technique, providing reliability, sensitivity, reproducibility, and also correlation to retinal ganglion cell loss, *see* Exhibit J.

Other limits and disadvantages of Goldman perimetry include (*see* Exhibits J and K):

1. Direction and speed of stimulus movement are guided by the examiner's hand and, therefore, are difficult to standardize. Thus, the results depend on the examiner's skills and may be confounded by examiner bias (in Okamoto II, it is not disclosed that the exams were performed in a masked fashion as it must be done for any clinical trial, therefore, the examiner bias must be considered of primary importance). Examiner dependence can be associated with poor reproducibility of results.

2. Goldman perimetry results, as being subjectively obtained, are notoriously difficult to quantify, and this is made even more difficult by the lack of standardization of equipment and method.

3. Goldman perimetry does not measure the depth of a scotoma (visual field defect). Because of the pantograph mechanism in the Goldmann instrument, the spatial resolution decreases with increasing eccentricity, which can give rise to a poor cartographic accuracy. Patients who repeat Goldman perimetry over time show an improvement due to a so-called "learning effect." This can be overcome only with computerized examinations when results are confirmed at least three times.

4. There are also other shortcomings of the Goldmann perimeter, such as lack of autocalibration, lack of permanent documentation of the test procedure used to determine individual visual field borders, and the inability to examine the area of 2° around the fixation point.

In view of the foregoing, Applicants submit that ANY conclusion can be drawn by a personal evaluation of a Goldman manual perimetry of a single patient. Accordingly, an ordinary artisan could not have reasonably predicted from Okamoto I or Okamoto II that NGF may be used to efficaciously treat glaucoma.

In view of the foregoing, Applicants submit that the amended claims are not rendered obvious by either Okamoto I or Okamoto II. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendment and remarks, Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Ph.D., Registration No. 46,046, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: _____

Respectfully submitted,

By_____
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Attachments